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DERIVATIVES OF 4,5-DIHYDRO-4-OXOFURAN-2-CARBOXYLIC ACID, PREPARATIONS AND USE THEREOF AND TETRAHYDROPYRAN-2,3,5-TRIONE INTERMEDIATES

This invention relates to novel derivatives of 4,5-dihydro-4-oxofuran-2-carboxylic acid, to therapeutically acceptable salts thereof, to processes for their preparation, to methods for using the derivatives, to pharmaceutical compositions containing the derivatives and to tetrahydropyran-2,3,5-trione intermediates used in the preparation of the derivatives.

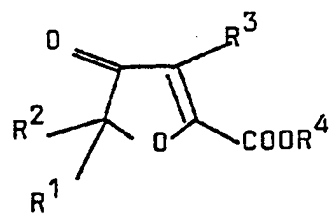
More specifically, the present invention relates to novel derivatives of 4,5-dihydro-4-oxofuran-2-carboxylic acid having two substituents at position 5 and in addition being optionally further substituted at position 3 with a lower alkyl group as well as esters thereof. These derivatives are useful as hypolipidemic agents in a mammal at dosages which do not elicit undesirable side effects.

4,5-Dihydro-4-oxofuran derivatives are extensively described in the literature. Additionally, derivatives of 4,5-dihydro-4-oxofuran-carboxylic acids have also been disclosed. For example, 4,5-dihydro-2-methyl-4-oxofuran-3-carboxylic acid and its ethyl ester are described by R.E.Rosenkranz _et al_., Helv, Chim. Acta., _46_, 1259(1963) and references cited therein. In addition, this reference discloses the structure of 4,5-dihydro-5-methyl-4-oxofuran-2-carboxylic acid as a hypothetical intermediate during the decarboxylation of 4-methoxy-5-methylfuran-2-carboxylic acid. The presence of 4,5-dihydro-5-methyl-4-oxofuran-2-carboxylic acid was not confirmed by isolation or other means.

Recently a few furan derivatives were reported to be hypolipidemic agents. More specifically, some derivatives of 2,3,4,5-tetrahydro-3-oxo-4-hydroxy-iminofurans, 2,5-dihydrofurans and 2,3,4,5-tetrahydrofurans are described to have weak to moderate hypolipidemic activity by G.B. Bennett _et al_., J. Med. Chem., _19_, 709 (1976). However, the latter report also states that the furan derivatives, disclosed therein, are devoid of a desirable level of hypolipidemic activity.

The 4,5-dihydro-4-oxofuran-2-carboxylic acid derivatives of this invention are novel compounds having hypolipidemic activity without affecting liver weight.

Accordingly this invention provides compounds of formula:



(I)

in which R^1 and R^2 each is lower alkyl, cyclo(lower)alkyl, lower alkoxy(lower)alkylene, phenyl or phenyl mono- or disubstituted with lower alkyl, lower alkoxy, halo, nitro or trifluoromethyl; or R^1 and R^2 together form a $-(CH_2)_m-X-(CH_2)_n-$ chain wherein m and n each is an integer from one to four and X is methylene, oxa or thia; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 or spiro[indan]-1 radical; R^3 is hydrogen or lower alkyl; and R^4 is hydrogen, lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl(lower)alkylene, or a therapeutically acceptable addition salt thereof.

A preferred group of compounds of formula I are those in which R^1 is lower alkyl, phenyl or phenyl monosubstituted with halo; R^2 is lower alkyl; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 radical; R^3 is hydrogen; and R^4 is hydrogen, lower alkyl or 3-pyridinyl(lower)alkylene, or a therapeutically acceptable addition salt thereof.

A most preferred group of compounds of formula I are those in which R^1 is lower alkyl, phenyl or 4-chlorophenyl; R^2 is lower alkyl; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 radical; R^3 is hydrogen; and R^4 is

hydrogen, lower alkyl or 3-pyridinyl methyl, or a therapeutically acceptable addition salt thereof.

The compounds of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen can be prepared by a process, which comprises:

cyclizing a compound of formula X

$$R^1\text{-}\underset{\displaystyle OH}{\overset{\displaystyle R^2}{C}}\text{-}CO\text{-}CH(R^3)\text{-}CO\text{-}COOH \qquad (X)$$

in which R^1, R^2 and R^3 are as defined herein under acidic conditions.

Compounds of formula I wherein R^4 is lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)-alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)-amino(lower)alkylene or 3-pyridinyl(lower)alkylene can be prepared by esterifying a compound of formula I wherein R^4 is hydrogen. More specifically, the compounds of formula I in which R^1, R^2, R^3 and R^4 are as defined herein can be prepared by a process, which comprises:

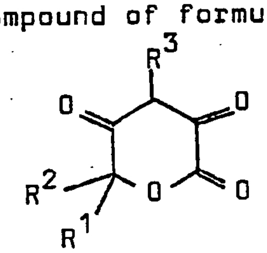
reacting a compound of formula II

$$R^1\text{-}\underset{\displaystyle OH}{\overset{\displaystyle R^2}{C}}\text{-}CO\text{-}CH_2R^3 \qquad (II)$$

in which R^1, R^2 and R^3 are as defined herein with a di(lower alkyl)oxalate in the presence of a strong inorganic proton acceptor under anhydrous conditions, hydrolyzing the mixture with water at pH 10 to 12, to give a compound of formula X and allowing the latter mixture to stand under acidic conditions to obtain the corresponding compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen; and if desired esterifying the latter compound of formula I

to obtain the corresponding compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene, or 3-pyridinyl(lower) -alkylene.

The compound of formula X may also be prepared by hydrolysing a compound of formula



(XI)

wherein R^1, R^2 and R^3 are as defined above, under aqueous alkaline conditions at pH 10 to 12, e.g. using KOH or NaOH, and then acidifying.

The compounds of formula I, or a therapeutically acceptable addition salt thereof, lower lipid levels in a mammal when administered to said mammal in an effective hypolipidemic amount.

A convenient form for administering the compounds involves a pharmaceutical composition comprising a compound of formula I or a therapeutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The term "lower alkyl" as used herein means straight chain alkyl radicals containing from one to six carbon atoms and branched chain alkyl radicals containing three or four carbon atoms and includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, n-hexyl and the like.

The term "lower alkoxy" as used herein means straight chain alkoxy radicals containing from one to six carbon atoms and branched chain alkoxy radicals containing three or four carbon atoms and include a methoxy, ethoxy, isopropoxy, n-butoxy, n-hexyloxy and the like.

The term "lower alkylene" as used herein means a divalent organic radical derived from either straight and branched chain aliphatic hydrocarbons containing from one to six carbon atoms by removal of two hydrogen atoms and includes methylene, ethylene, 1-methylpropylene, 2-methylpropylene, 2-ethylpropylene, 2-butylethylene and the like.

The term "cyclo(lower)alkyl" as used herein means saturated cyclic hydrocarbon radicals containing from three to six carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "lower alkanol" as used herein means both straight and branched chain alkanols containing from one to four carbon atoms and includes methanol, ethanol, isopropanol, butanol and the like.

The term "strong inorganic proton acceptor" as used herein means the inorganic bases, preferably the alkali metals, the alkali metal hydrides, amides, hydroxides and alkoxides, for example, sodium, sodium hydroxide, potassium hydroxide, sodium ethoxide, sodium methoxide, sodium hydride and the like.

The term "lower alkanoyl" as used herein means straight chain alkanoyl radicals containing from two to six carbon atoms and a branched chain alkanoyl radical containing four carbon atoms and includes acetyl, propionyl, isobutyryl, n-hexanoyl and the like.

The term "organic proton acceptor" as used herein means the organic bases, or amines for instance, triethylamine, pyridine, N-ethylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene and the like.

The term "therapeutically acceptable addition salt" as used herein includes the therapeutically acceptable acid addition salts of the compound of formula I in which R^4 is amino(lower)alkylene, lower alkylamino(lower)-alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl(lower)alkylene. The acid addition salts are prepared by reacting the base form of the appropriate

compound of formula I with one or more equivalents, preferably with an excess, of the appropriate acid in an organic solvent, for example, diethyl ether or an ethanol-diethyl ether mixture. These salts, when administered to a mammal, possess the same pharmacologic activities as the corresponding bases. For many purposes it is preferable to administer the salts rather than the base compounds. Suitable acids to form these salts include the common mineral acids, for instance hydrohalic, sulfuric or phosphoric acid; as well as the organic acids, for instance, formic, acetic, maleic, malic, ascorbic, succinic, fumaric, citric, or tartaric acid; or acids which are sparingly soluble in body fluids and which impart slow-release properties to their respective salts such as pamoic or tannic acid or carboxymethyl cellulose.

The addition salts thus obtained are the functional equivalent of the parent base compound in respect of their therapeutic use. Hence, these addition salts are included within the scope of this invention and are limited only by the requirement that the acids employed in forming the salts be therapeutically acceptable.

Furthermore, the term "therapeutically acceptable addition salt" as used herein also includes the therapeutically inorganic or organic base addition salts of the compound of formula I in which R^4 is hydrogen, i.e. compound of formula I which are acids. These derived salts possess the same activity as the parent acid and are included within the scope of this invention. The acid is transformed in excellent yield into the corresponding therapeutically acceptable salt by neutralization of said acid with the appropriate inorganic or organic base. The salts are administered in the same manner as the parent acid compounds. Suitable inorganic bases to form these salts include, for example, the hydroxides, carbonates, bicarbonate or alkoxides of the alkali metals or alkaline earth metals, for example, sodium, potassium, magnesium, calcium and the like. Suitable organic bases

include the following amines; lower mono-, di- and trialkylamines, the alkyl radicals of which contain up to three carbon atoms, such as methylamine, dimethylamine, trimethylamine, ethylamine, di- and triethylamine, N-methyl-N-ethylamine, and the like; mono-, di and trialkanolamines, the alkanol radicals of which contain up to three carbon atoms, for example, mono-, di- and triethanolamine alkylene-diamines which contain up to six carbon atoms, such as hexamethylenediamine; phenylalkylamines, for example, benzylamine, phenylethylamine and N-methyl-phenylethylamine; cyclic saturated or unsaturated bases containing up to six carbon atoms, such as pyrrolidine, piperidine, morpholine, piperazine and their N-alkyl and N-hydroxyalkyl derivatives, such as N-methyl-morpholine and N-(2-hydroxyethyl)-piperidine, as well as pyridine. Furthermore, there may be mentioned the corresponding quaternary salts, such as the tetraalkyl (for example tetramethyl), alkyl-alkanol (for example methyltri-methanol and trimethyl-monoethanol) and cyclic ammonium salts, for example the N-methylpyridinium, N-methyl-N-(2-hydroxyethyl)-morpholinium, N,N-dimethylmorpholinium, N-methyl-N-(2-hydroxyethyl)-morpholinium, N,N-dimethyl-piperidinium salts, which are characterized by having good water-solubility. In principle, however, there can be used all the ammonium salts which are physiologically compatible.

The transformations to the salts can be carried out by a variety of methods known in the art. For example, in the case of the inorganic salts, it is preferred to dissolve the acid of formula I in water containing at least one equivalent amount of hydroxide, carbonate, or bicarbonate corresponding to the inorganic salt desired. Advantageously, the reaction is performed in a water-miscible, inert organic solvent, for example, methanol, ethanol, dioxane and the like in the presence of water.

For example, such use of sodium hydroxide, sodium carbonate or sodium bicarbonate gives a solution of the sodium salt. Evaporation of the solution or addition of a water miscible solvent of a more moderate polarity, for example, a lower alkanol, for instance, butanol, or a lower alkanone, for instance, ethyl methyl ketone, gives the solid inorganic salt if that form is desired.

To produce an amine salt, the acidic compound of formula I is dissolved in a suitable solvent of either moderate or lower polarity, for example, ethanol, methanol, ethyl acetate, diethyl ether and benzene. At least an equivalent amount of the amine corresponding to the desired cation is then added to that solution. If the resulting salt does not precipitate, it can usually be obtained in solid form by addition of a miscible diluent of low polarity, for example, benzene or petroleum ether, or by evaporation. If the amine is relatively volatile, any excess can easily be removed by evaporation. It is preferred to use substantially equivalent amounts of the less volatile amines.

Salts wherein the cation is quaternary ammonium are produced by mixing the acid of formula I with an equivalent amount of the corresponding quaternary ammonium hydroxide in water solution, followed by evaporation of the water.

Also included in this invention are the stereochemical isomers of the compounds of formula I and XI which result from asymmetric centres, contained therein. It is to be understood that all isomers and mixtures thereof arising from such asymmetry are included within the scope of this invention. When two asymmetric centres are present diastereomers are obtainable in substantially pure form by classical separation techniques and by sterically controlled synthesis.

Individual enantiomers are included. These can be separated by fractional crystallization of the diastereomeric salts thereof.

The compounds of formula I, or a therapeutically acceptable salt thereof, are useful hypolipidemic agents in a mammal upon oral or parenteral administration. Their hypolipidemic properties are readily demonstrated by the following method: male albino rats (eight rats per group), weighing 140-170g are given a single daily oral dose of the test compound by gavage as a suspension in 2% Tween-80 in water (1.0 ml). (TWEEN is a Registered Trade Mark). In the same manner, controls are given only 2% Tween-80 in water (1.0 ml) daily. After one week of treatment, animals are decapitated and the blood is collected. The serum is separated by centrifugation and serum cholesterol levels are measured by the method of A. Zlatkis et al., J.Lab.Clin. Med., 41, 486 (1953), as modified for the autoanalyser (Method Np-24). Serum phospholipids are determined by the semi-automated technique of M.Kraml, Clin. Chim. Acta., 13, 442 (1966) and serum triglycerides are measured by the semiautomated method of M.Kraml and L.Cosyns, Clin. Biochem., 2, 373 (1959). The activity of a test compound is assessed by comparing serum cholesterol, phospholipid and/or triglyceride levels in rats treated with the test compound and control rats and the data are analysed for significance by the Student's t-test. The following results demonstrating hypotriglyceridemic activity are calculated by subtracting the serum triglyceride level in treated rats from the control serum triglyceride level, and expressing the difference as a percentage of the control level. The following compounds of formula I at a dose of 1.0 mmole per kilogram of body weight per day lower triglyceride levels by the indicated percentage: 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid (42%, described in Example 4), 4,5-dihydro-5(1-methylethyl)-4-oxo-5-phenylfuran-5-carboxylic acid (53%, described in Example 4), 4,5-dihydro-5,5-dimethyl-4-oxofuran-2-carboxylic acid (37%, described in Example 4), sprio[furan-5(4H),1'(2'H)-naphthalene]-3',4'-dihydro-4-oxo-2-carboxylic acid (43%,

described in Example 4), 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid methyl ester (53%, described in Example 5) and 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid 3-pyridinylmethyl ester (61%, described in Example 6).

The compounds of formula I, or a therapeutically acceptable salt thereof, can be used also in combination with known hypolipidemic agents, for example, clofibrate, for reduction of elevated lipids in a mammal. When used in this combination, the compound of formula I can be administered sequentially or simultaneously in combination with an effective amount of the known hypolipidemic agent. Suitable methods of administration, compositions and dosages of clofibrate (ATROMID-S) is described by Charles E. Baker, Jr. "Physician's Desk Reference", Medical Economics Company, Oradell, N.J. 1977, pp 593-594, for example, 0.5 to 2.0 g per patient per day in divided dosages. The compounds of formula I, or a therapeutically acceptable salt thereof, in combination with a known hypolipidemic agent, are used in the same manner as described herein for their use as hypolipidemic agents.

When the compounds of formula I of this invention are used as hypolipidemic agents in a mammal, e.g. rats and dogs, they are used alone or in combination with pharmacologically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice. For example, they are administered orally in solid form, e.g. capsule or tablet. They are also administered orally in the form of suspension or solutions, or they may be injected parenterally. For parenteral administration they may be used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic.

The tablet compositions for oral administrations contain the active ingredient in admixture with non-toxic

pharmaceutical excipients known to be suitable in the manufacture of tablets. Suitable pharmaceutical excipients are, for example, starch, milk sugar, certain types of clay and so forth. The tablets can be uncoated or they can be coated by known techniques so as to delay disintegration and absorption in the gastroinestinal tract and thereby provide a sustained action.

The aqueous suspensions for oral use of the compounds of the invention contain the active ingredient in admixture with one or more non-toxic pharmaceutical excipients, for instance, emulsifying and suspending agents, known to be suitable in the manufacture of aqueous suspensions. Suitable excipients are, for example, methyl-cellulose, sodium alginate, gum acacia, lecithin and so forth. The aqueous suspensions can also contain one or more preservatives, one or more colouring agents and/or one or more sweetening agents.

Non-aqueous suspensions for oral use can be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil, or coconut oil; or in mineral oil. The suspension can contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. These compositions can also contain a sweetening agent, flavouring agent and antioxidant.

For parenteral administration, which includes intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention can be used in the form of a sterile solution, wherein the pH should be suitably adjusted and buffered. The solution can contain other pharmaceutical excipients, for example, enough saline or glucose to make the solution isotonic.

The dosage of a compound of formula I of this invention as a hypolipidemic agent will vary with the form of administration and the particular host as well as the age and condition of the host under treatment. Generally, treatment is initiated with small dosages substantially less than the optimal dose of the compound. Thereafter,

the dosage is increased by small increments until the optimal effect under the circumstances is reached. In general, a compound of this invention is most desirably administered at a concentration that will generally afford effective results without causing any harmful or deleterious side effects. The effective hypolipidemic amount of the compound usually ranges from about 1.0 mg to about 500 mg per kilogram of body weight per day, although as aforementioned variations will occur. However, a dosage level that is in the range of from about 5 mg to about 300 mg per kilogram of body weight per day is employed most desirably in order to achieve effective results.

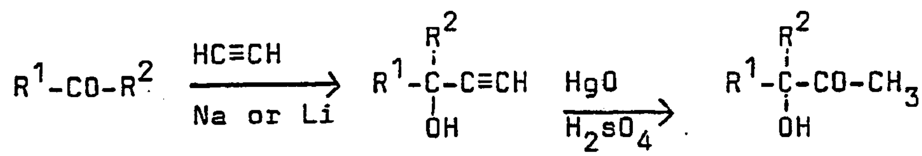
For the preparation of the 4,5-dihydro-4-oxofuran-2-carboxylic acid derivatives of formula I the preferred starting materials are the α-hydroxyketones of formula II

$$R^1\text{-}\underset{\displaystyle OH}{\overset{\displaystyle R^2}{C}}\text{-CO-}CH_2R^3 \qquad \text{(II)}$$

in which R^1 and R^2 each is lower alkyl, cyclo(lower)alkyl, lower alkoxy(lower)alkylene, phenyl or phenyl mono- or disubstituted with lower alkyl, lower alkyl, lower alkoxy, halo, nitro or trifluoromethyl; or R^1 and R^2 together form a $-(CH_2)_m-X-(CH_2)_n-$ chain wherein m and n each is an integer from one to four and X is methylene, oxa or thia; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 or spiro[indan]-1 radical; and R^3 is hydrogen or lower alkyl.

The starting materials of formula II in which R^1 and R^2 are as defined herein and R^3 is hydrogen are either known or they can be prepared as is illustrated in reaction scheme 1.

Reaction Scheme 1



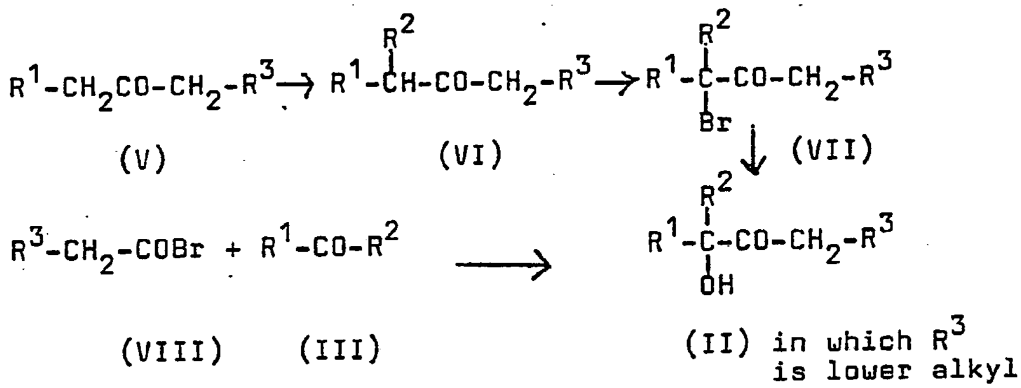
(III) (IV) (II) in which R^3 is hydrogen

With reference to reaction scheme 1, a number of acetylenic carbinols of formula IV are known and commercially available. Alternatively, acetylenic carbinols are readily available from addition of a metallic acetylide to the ketone of formula III in which R^1 and R^2 are as defined herein using the method described by A.W.Johnson, Acetylenic Compounds, Vol. 1, The Acetylenic Alcohols, E. Arnold Co., London, 1946; R.A.Raphael, Acetylenic Compounds in Organic Synthesis, London, Butterworth's Sci. Publ., 1955; P.A.Robins and J.Walker, J. Chem. Soc., 177 (1957); and E.D.Bergmann et al., J.Appl. Chem. 3, 39(1953). In the preferred method a mixture of the compound of formula III and lithium or sodium in a solution of anhydrous liquid ammonia saturated with gaseous acetylene is allowed to react for nine hours and the corresponding compound of formula IV is isolated.

The acetylenic carbinols of formula IV are converted to the corresponding α-hydroxyketones of formula II, by hydration of the acetylenic carbinol in a mixture of mercuric oxide (red form) or mercuric sulfate, aqueous tetrahydrofuran and sulfuric acid at 60-65°C for one to six hours, according to the procedure described by A.W. Johnson, cited above pp 102-105; E.D.Bergmann and D.F. Herman, J. Appl. Chem., 3, 42(1953), G.F.Hennian and B.R.Fleck, J. Amer. Chem. Soc., 77, 3253 (1955); and G.F.Hennian and E.J.Watson, J. Org. Chem., 23,656(1958).

The starting materials of formula II in which R^1 and R^2 are as defined herein and R^3 is lower alkyl are either known or they can be prepared as is illustrated in reaction scheme 2.

Reaction Scheme 2



With reference to reaction scheme 2, an organometallic derivative of the compound of formula VIII is condensed with the ketone of formula III to obtain the corresponding α-hydroxyketone of formula II in which R^3 is lower alkyl according to the conditions described by I.I.Lapkin and T.N.Povarnitsyna, Zh. Obshch. Khim., 38,99(1968), cf. Chem. Abstr., 69, 19233z.

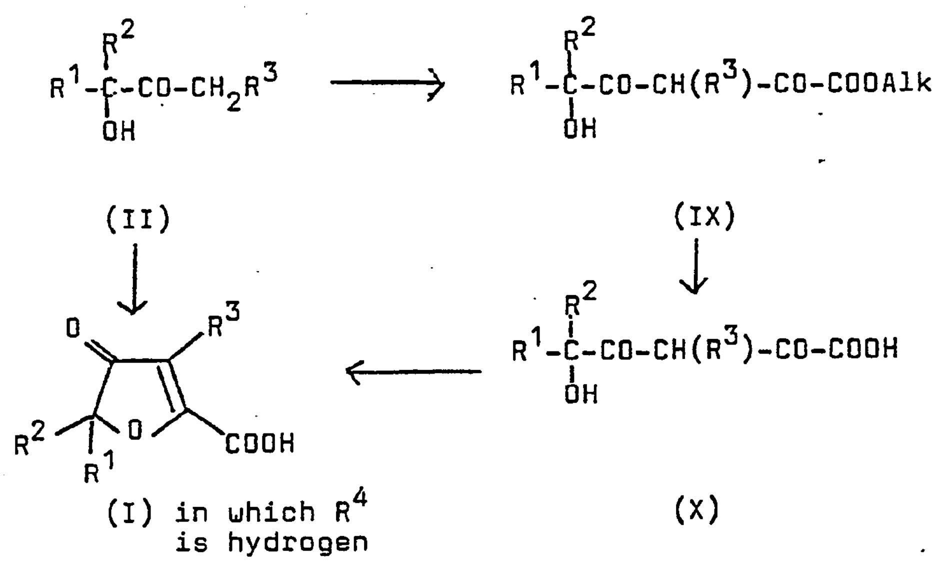
The alternative route starting from the compound of formula V is especially suitable for preparing the α-keto alcohols of formula II in which R^1 or R^2 is phenyl or phenyl mono- or disubstituted with lower alkyl, lower alkoxy, halo, nitro or trifluoromethyl. Alkylation of the compound of formula V, using the method of K.Binovic and S. Vrancea, Chem. Ther., 313(1968), gives the corresponding compound of formula VI. The latter compound is brominated, according to the conditions described by J.R.Catch *et al.*, J. Chem. Soc. 272(1948), to obtain the corresponding bromo-ketone of formula VII. Conversion of the latter bromoketone to the corresponding α-hydroxyketone of formula II is described by J.G.Aston and R.B.Greenberg,

J. Amer. Chem. Soc., 62, 2590(1940); J. Kapron and J. Wiemann, Bull. Soc. Chim. France, 12, 945(1945); and Y.L. Pascal, Ann. Chim. (Paris), 245(1968).

In addition to the above described preparations, α-hydroxyketones of formula II can be prepared by methods described by Y.L.Pascal, cited above and P. Kaufmann, J. Amer. Chem. Soc., 26, 5794(1954).

Reaction scheme 3 illustrates the conversion of the α-hydroxyketone of formula II to the corresponding compound of formula I in which R^1, R^2 and R^3 are as defined herein.

Reaction Scheme 3



As illustrated by reaction scheme 3, the compound of formula I in which R^4 is hydrogen is prepared from the compound of formula II via the route II→IX→X→I. Although the intermediates of formula IX and X can be isolated and further reacted in separate steps, the compound of formula II can be converted to the corresponding compound of formula I via intermediates IX and X in a single reaction vessel without isolating the latter intermediates.

The first step in the conversion of the α-hydroxyketone of formula II is the condensation of substantially equimolar amounts of the α-hydroxyketone and a di(lower alkyl)oxalate, preferably dimethyl or diethyl oxalate, in the presence of one to four molar equivalents of a strong inorganic proton acceptor, preferably sodium hydride, in an anhydrous inert organic solvent. Preferred inert organic solvents can be selected from the di(lower alkyl)-ethers or cyclic ethers, for example, diethyl ether, dioxane and tetrahydrofuran. The reaction mixture is maintained at 30 to 70°C, preferably 50 to 60°C, for 10 to 30 hours. The resultant enolate salt is filtered as rapidly as possible, dissolved in water, acidified with a diluted inorganic acid, and the corresponding compound of formula IX is extracted with an inert water immiscible organic solvent, preferably diethyl ether.

Hydrolysis of the latter compound is readily achieved under alkaline conditions, for example with a solution of one to three molar equivalents of potassium or sodium hydroxide in an aqueous solution of a water miscible organic solvent, preferably methanol, ethanol, tetrahydrofuran or dioxane, at 15 to 30°C for 15 to 40 hours. The aqueous solution is washed with a water immiscible organic solvent, preferably diethyl ether, benzene, chloroform, dichloromethane and the like. The pH of the aqueous solution is adjusted to 3 to 5 with a strong acid, e.g. hydrochloric or sulfuric acid. Thereafter, the corresponding compound of formula X is obtained by extraction of the aqueous solution with a water immiscible organic solvent, for example one of the previously noted organic solvents.

The latter compound can be cyclized under acidic conditions to obtain the corresponding compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen. In one method of achieving this cyclization, a solution of the compound of formula X and 0.1 to 10 molar equivalents, preferably 0.1 to 0.4 molar equivalents, and

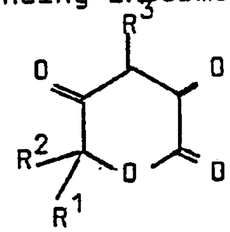
an acid catalyst, for example, hydrogen chloride, hydrogen bromide, hydrochloric acid, hydrobromic acid, p-toluenesulfonic acid, sulfuric acid, phosphoric acid, polyphosphoric acid and the like, preferably p-toluenesulfonic acid or hydrogen chloride, in an inert organic solvent, preferably benzene or toluene, is maintained at 20 to 100°C for two to 50 hours. In another method, the compound of formula X is cyclized in an aqueous solution containing the acid catalyst at 10 to 50°C for 10 to 50 hours. Preferred acid catalysts for use in the aqueous conditions can be selected from hydrochloric acid, sulfuric acid, hydrobromic acid and phosphoric acid. The aqueous solution usually requires sufficient acid catalyst so that the solution is maintained at pH 0.5 to 3.0 preferably 1.0 to 2.0.

In a modification of the conversion of the compound of formula II to the corresponding compound of formula I, the above individual steps of condensation, alkaline hydrolysis and cyclization are combined in a process wherein the intermediates of formula IX and X are not isolated.

In this modification, the α-hydroxyketone of formula II is condensed with a di(lower alkyl) oxalate in the same manner as described above. However, the reaction mixture is not filtered but instead is mixed with about an equal volume of water. The resulting aqueous alkaline solution is, if required, adjusted to pH 10 to 12 with, for example, sodium hydroxide and maintained at pH 10 to 12 and at 15 to 30°C for 10 to 40 hours and washed with a water immiscible organic solvent, preferably diethyl ether or benzene. An acid catalyst, preferably hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid, is added to the aqueous solution until the solution reaches pH 0.5 to 3.0, preferably 1.0 to 2.0. The acidic solution is maintained at 10 to 50°C, preferably 20 to 30°, for 0.5 to 10 hours and extracted with a water immiscible organic solvent, for example, ethyl acetate, diethyl ether, benzene, toluene, chloroform, dichloromethane and the like. The organic extract is evaporated and, if required, purified to obtain

the corresponding compound of formula I in which R^4 is hydrogen.

If the aqueous alkaline solution in the latter preparation is maintained at pH 8 to 9 instead of pH 10 to 12, a corresponding intermediate of formula XI



(XI)

in which R^1, R^2 and R^3 are as defined herein can be isolated after acidification of the aqueous alkaline solution. More specifically, the α-hydroxyketone of formula II is condensed with a di(lower alkyl)oxalate in the same manner as described above. The reaction mixture is not filtered but instead is mixed with about an equal volume of water and if necessary the resulting aqueous solution is adjusted to pH 8 to 9, for example, with dilute hydrochloric acid or sodium hydroxide. The resulting aqueous solution is preferably maintained at pH 8 to 9 and at 15 to 30°C for one to five hours and washed with a water immiscible organic solvent, in the same manner as described above. The mixture is acidified, maintained at 10 to 50°C, preferably 20 to 30°C, for one to 30 minutes and extracted, in the same manner as described above for II→I, to obtain the corresponding intermediate of formula XI.

Reaction of the intermediate of formula XI under aqueous alkaline conditions at pH 10 to 12 gives the corresponding compound of formula I in which R^4 is hydrogen. For this reaction, a solution of the compound of formula II in aqueous potassium or sodium hydroxide is maintained at pH 10 to 12 and at 15 to 30°C for 10 to 40 hours and washed with a water immiscible organic solvent, in the same manner as described above. Subsequently, acidification of the aqueous solution, maintenance of the acidic solution and extraction, in the same manner as described above for II→I,

gives the corresponding compound of formula I in which R^4 is hydrogen.

Compoundsof formula XI in which R^1, R^2 and R^3 are as defined herein are also included within this invention.

The acidic compound of formula I in which R^4 is hydrogen is esterified to obtain the corresponding ester of formula I in which R^4 is lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl(lower)alkylene. A number of esterification methods can be used, for example, mixed anhydride; dehydrative coupling reagents, for instance, dicyclohexylcarbodiimide; acid catalysts: diazoalkanes; and acid chloride.

A preferred method of esterification employs an acid catalyst, preferably 0.1 to 1.0 molar equivalents of anhydrous sulfuric acid or hydrogen chloride, and 2 to 50 equivalents of a lower alkanol, hydroxycyclo(lower)alkane, phenyl(lower)alkanol, amino(lower)alkanol, lower alkylamino-(lower)alkanol, di(lower alkyl)amino(lower)alkanol or 3-pyridinyl(lower)alkanol at 50 to 100°C for one to ten hours. It should be noted that when amino(lower)alkanol, lower alkylamino(lower)alkanol, di(lower alkyl)amino(lower)alkanol or 3-pyridinyl(lower)alkanol is used, then a corresponding additional molar mount of the acid catalyst should be present in the reaction vessel. If the reactants are mutually soluble, a solvent for the esterification can be omitted. Otherwise, any anhydrous inert organic solvent can be used, for example, dimethylformamide, benzene, toluene, chloroform and the like.

Another preferred method of esterification proceeds through the acid chloride. In this method, a solution of the acidic compound of formula I in which R^4 is hydrogen and 5 to 50 molar equivalents of thionyl chloride is heated at 50 to 80°C for one to ten hours and evaporated to obtain the corresponding acid chloride. A solution of the latter acid chloride, one to ten molar equivalents of the above

noted alcohols and an organic proton acceptor, for example, pyridine or triethylamine, in an inert organic solvent, for example, acetone, benzene, dichloromethane, toluene, chloroform or dimethylformamide, preferably acetone, is maintained at 0 to 50°C for two to ten hours. Evaporation and purification affords the compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)-alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)-amino(lower)alkylene or 3-pyridinyl(lower)alkylene.

The following examples illustrate further this invention.

EXAMPLE 1

3-Hydroxy-4-methyl-3-phenyl-1-pentyne (IV:R^2 =$CH(CH_3)_2$ and R^1 = Ph)

A reaction flask, equipped with a dry-ice reflux condenser, is charged with 700 ml of freshly condensed liquid ammonia. The ammonia gas is passed through a tower of potassium hydroxide pellets. Upon stirring, a rapid stream of acetylene gas (dried in a sulfuric acid wash bottle) is introduced into the ammonia for 10 min, then the rate of passage of the acetylene is reduced and a continuous flow of acetylene through the reaction mixture is maintained during the following operations (approx. 9 hr.). Small pieces of sodium (9.2 g) are inserted, and 2 hr later, 2-methyl-1-phenyl-1-propanone (50 g) is added dropwise. The stirring is continued for 6 hr at -33^oC then, the stream of acetylene is shut off, and the ammonia is allowed to evaporate in the hood (overnight). After adding cautiously ice-water, the resultant solution is acidified with diluted sulfuric acid, and extracted with diethyl ether. The combined extracts are washed with saturated brine, dried over magnesium sulfate, filtered, and evaporated to yield 45.5 g of the title compound, ir ($CHCl_3$) 3600, 3310, 1450, and 1010 cm^{-1} and nmr ($CDCl_3$) δ 0.85 and 1.07 (d), 2.10(heptuplet), 2.35(s), 2.66(s), 7.27(m) and 7.55(m).

EXAMPLE 2

3-Hydroxy-4-methyl-3-phenyl-2-pentanone (II: R^2 = $CH(CH_3)_2$, R^1 = Ph

To a refluxing mixture of tetrahydrofuran (70 ml), water (5 ml), and conc. sulfuric acid (1.5 g) is added 1 g of red mercuric oxide and the reflux is continued for 5 min. Then,the inside temperature is adjusted to 60-62^oC and 10 g of 3-hydroxy-4-methyl-3-phenyl-1-pentyne

(described in Example 1) is added. The reaction is exothermic (spontaneous mild reflux) and there is a noticeable clearing of the mixture. Another 1 g of mercuric oxide is added, and the solution is refluxed for 30 min. The reaction mixture is stirred at 60°C for an additional 3 hr, during which time the precipitation of a mercury sludge occurred. After cooling, the slurry is diluted with 100 ml of diethyl ether and filtered through diatomaceous earth. The filter cake is washed with 200 ml of diethyl ether, and the combined filtrates are washed repeatedly with water, dried over magnesium sulfate, filtered, and evaporated to give 10.6 g of the title product, ir ($CDCl_3$) 3470 and 1715-1710 cm^{-1} and nmr ($CDCl_3$) δ 0.91(d), 2.15(s), 2.79(heptuplet), 4.39(s) and 7.20-7.65(m).

EXAMPLE 3

3-Hydroxy-3-phenyl-2-butanone(II:R^2 = Me, R^1 = Ph and R^3 = H).

The title compound is prepared by using a modified method of G.F.Hennion and B.R.Fleck, J.Amer.Chem.Soc., 77, 3258(1955). To a mixture of methanol (5 ml), water (0.2 ml), sulfuric acid (100 mg), and mercuric sulfate (100 mg) is added at 55°C a solution of 3-hydroxy-3-phenyl-1-butyne (2 g) in 90% aqueous methanol (5 ml) over a period of 90 min. The reaction is slightly exothermic, and the inside temperature is maintained at 55-57°C. During the reaction time, 50 mg of mercuric sulfate is added. When addition of the acetylenic component is complete, another portion (50 mg) of mercuric sulfate is added, and the mixture is stirred at 55°C for 1 hour. During this time 1 ml of water is added. After cooling, the reaction mixture is poured into ice-water and extracted with diethyl ether. The combined extracts are washed with water, dried over magnesium sulfate, filtered and evaporated. The resultant oil is chromatographed on silica gel using

benzene. The appropriate eluates are evaporated to give 0.5g of the title compound, ir($CHCl_3$)3450 and 1751 cm^{-1} and nmr($CDCl_3$) δ 1.75(s), 2.08(s), 4.50(s) and 7.40(m).

In the same manner but replacing 3-phenyl-3-hydroxy-1-butyne with an equivalent amount of 3-hydroxy-3-(4-chlorophenyl)-1-butyne, 3-hydroxy-3-methyl-1-butyne, 1-ethynyl-1,2,3,4-tetrahydronaphthalene, 3-ethyl-3-hydroxy-1-heptyne, 3-hydroxy-3, 3-diphenyl-1-propyne, 3-cyclohexyl-3-hydroxy-1-hexyne, 4-ethoxy-3-(3-methoxyphenyl)-3-hydroxy-1-butyne, 3-(3,4-diethylphenyl)-3-hydroxy-3-(4-nitrophenyl)-1-propyne, 3-ethynyl-3-hydroxytetrahydrofuran, 1-ethynyl-1-hydroxycyclohexane, 1-ethynyl-1-hydroxyindane or 3-cyclopentyl-5-ethoxy-3-hydroxy-1-pentyne, the following compounds of formula II are obtained, respectively: 3-hydroxy-3-(4-chlorophenyl)-2-butanone, ir ($CHCl_3$)3440 and 1710 cm^{-1}, 3-hydroxy-3-methyl-2-butanone, 1-acetyl-1-hydroxy-1,2,3,4-tetrahydronaphthalene ir(film) 3450 and 1710 cm^{-1}, 3-ethyl-3-hydroxy-2-heptanone, 3-hydroxy-3,3-diphenyl-2-propanone, 3-cyclohexyl-3-hydroxy-2-hexanone, 4-ethoxy-3-(3-methoxyphenyl)-3-hydroxy-2-butanone, 3-(3,4-diethylphenyl)-3-hydroxy-3-(4-nitrophenyl)-2-propanone, 3-acetyl-3-hydroxytetrahydrofuran, 1-acetyl-1-hydroxycyclohexane, 1-acetyl-1-hydroxyindane and 3-cyclopentyl-5-ethoxy-3-hydroxy-2-pentanone.

EXAMPLE 4

4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid(I:R^2 = Me, R^1 = Ph, and R^3 and R^4 = H)

(a) To a stirred suspension of sodium hydride (10.5 g, 54% in mineral oil) in dry tetrahydrofuran (400 ml) is added dropwise a solution of diethyl oxalate (16 g) and 3-hydroxy-3-phenyl-2-butanone (16.4 g described in Example 3) in tetrahydrofuran (50 ml). The solution temperature is maintained at 55-60°C, and the solution is maintained at this temperature for 18 hr after the

addition is complete. The cold reaction mixture is poured into water, the mixture is adjusted to pH 11 with sodium hydroxide and allowed to stand for 24 hours, and washed with diethyl ether. Upon addition of 6N hydrochloric acid, the aqueous solution is adjusted to pH 1. The acidic mixture is kept at 20 to 30^{o}C for 2 hours and extracted with diethyl ether. The ether extract is dried and slowly evaporated to obtain crystals (20 g) of the title compound, mp 174-176^{o}C. ANAL: Calculated for $C_{12}H_{10}O_4$: C, 66.06; H, 4.62%; Found: C, 66.41; H, 4.69%.

(b) A solution of the title compound in diethyl ether and a solution of an equimolar amount of benzylamine in diethyl ether are mixed at 0^{o}C. The precipitate is collected by filtration and crystallized from isopropanol to obtain the benzylamine salt of the title compound, m.p. 192-193^{o}C.

(c) In the same manner but replacing 3-hydroxy-3-phenyl-2-butanone with an equivalent amount of another compound of formula II described in Examples 2 and 3, the following compounds of formula I are obtained, respectively: 4,5-dihydro-5-(1-methylethyl)-4-oxo-5-phenylfuran-2-carboxylic acid, mp 151-153^{o}C and nmr($CDCl_3$) δ 0.77(d), 1.01(d), 2.85 (heptuplet), 6.03(s), 6.45(s) and 7.33(m); 5-(4-chlorophenyl)-4,5-dihydro-5-methyl-4-oxofuran-2-carboxylic acid, mp 169^{o}C and nmr ($CDCl_3$) δ 1.75(s), 6.25(s) and 7.45(m); 4,5-dihydro-5,5-dimethyl-4-oxofuran-2-carboxylic acid, mp 180-181^{o}C and ir (nujol) 2800(broad), 1737, 1670 and 1600 cm^{-1}; spiro[furan-5(4H), 1'(2'H)-naphthalene]-3',4'-dihydro-4-oxo-2-carboxylic acid, mp 152-154^{o}C and nmr (MeOH-d_4) δ 2.07(m), 2.84(t), 6.29(s) and 6.8-7.4(m); 5-butyl-5-ethyl-4,5-dihydro-4-oxofuran-2-carboxylic acid; 4,5-dihydro-4-oxo-5,5-diphenylfuran-2-carboxylic acid; 5-cyclohexyl-4, 5-dihydro-4-oxo-5-propylfuran-2-carboxylic acid; 4,5-dihydro-5-ethoxymethyl-5-(3-methoxyphenyl)-4-oxofuran-2-carboxylic acid; 4,5-dihydro-5-(3,4-diethylphenyl)-5-(4-nitrophenyl)-4-oxofuran-2-carboxylic acid;

1,7-dioxaspiro[4,4]non-2-ene-4-oxo-2-carboxylic acid; 1-oxaspiro[4,5]dec-2-ene-4-oxo-2-carboxylic acid; spiro-[furan-5(4H), 1'-indan]-4-oxo-2-carboxylic acid; and 5-cyclopentyl-4,5-dihydro-5-(3-ethoxypropyl)-4-oxofuran-2-carboxylic acid.

EXAMPLE 5

4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic Acid Methyl Ester (I:R^2 and R^4 = Me, R^1 = Ph and R^3 = H)

(a) A mixture of 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid (0.4 g, described in Example 4), absolute methanol (50 ml), and sulfuric acid (3 drops) is refluxed overnight and evaporated. The residue is diluted with 50 ml of diethyl ether, and the solution is washed quickly with saturated sodium bicarbonate and water, dried over magnesium sulfate, filtered, and evaporated. The residue is crystallized from diethyl ether to obtain the title compound (0.32 g) mp 60-62°C and nmr ($CDCl_3$) δ 1.81(s), 3.99(s), 6.25(s) and 7.42(m).

(b) In the same manner but replacing methanol with an equivalent amount of ethanol, propanol or butanol, the following compounds of formula I are obtained, respectively: 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid ethyl ester, 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid propyl ester and 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid butyl ester.

Similarly, but replacing 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid with an equivalent amount of another compound of formula I described in Example 4, the following compounds of formula I are obtained, respectively: 4,5-dihydro-5-(1-methylethyl)-4-oxo-5-phenylfuran-2-carboxylic acid methyl ester; 5-(4-chlorophenyl)-4,5-dihydro-5-methyl-4-oxofuran-2-carboxylic acid methyl ester; 4,5-dihydro-5,5-dimethyl-4-oxofuran-2-carboxylic acid methyl ester, mp 66°C, ir($CHCl_3$)1720, 1695 and 1575 cm^{-1}; spiro[furan-5(4H), 1'(2'H)-naphthalene]-3',4'-

dihydro-4-oxo-2-carboxylic acid methyl ester; 5-butyl-5-ethyl-4,5-dihydro-4-oxofuran-2-carboxylic acid methyl ester; 4,5-dihydro-4-oxo-5,5-diphenylfuran-2-carboxylic acid methyl ester; 5-cyclohexyl-4,5-dihydro-4-oxo-5-propylfuran-2-carboxylic acid methyl ester; 4,5-dihydro-5-ethoxymethyl-5-(3-methoxyphenyl)-4-oxofuran-2-carboxylic acid methyl ester; 4,5-dihydro-5-(3,4-diethylphenyl)-5-(4-nitrophenyl)-4-oxofuran-2-carboxylic acid methyl ester; 1,7-dioxaspiro[4,4]non-2-ene-4-oxo-2-carboxylic acid methyl ester; 1-oxaspiro[4,5]dec-2-ene-4-oxo-carboxylic acid acid methyl ester; spiro[furan-5-(4H), 1'-indan]-4-oxo-2-carboxylic acid methyl ester; and 5-cyclopentyl-4,5-dihydro-5-(3-ethoxypropyl)-4-oxofuran-2-carboxylic acid methyl ester.

EXAMPLE 6

4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic Acid 3-Pyridinylmethyl Ester (I:R^2 = Me, R^1 = Ph, R^3 = H and R^4 = 3-pyridinylmethyl).

(a) A mixture of 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid (8.75 g, described in Example 4) and thionyl chloride (90 ml) is refluxed for 3 hr and evaporated. The residue is dissolved in benzene (100 ml) and evaporated (twice.) The infrared spectrum of the residue is indicative of a quantitative conversion of the carboxylic acid into the carbonyl chloride, ir ($CHCl_3$) 1820 and 1795, 1755 and 1715 cm^{-1}. This material is dissolved in 50 ml of dry acetone and added to a mixture of 3-pyridinemethanol (4.8 g), pyridine (3.1 g), and acetone (100 ml) at 0^oC. The reaction mixture is stirred at 20 to 30^oC temperature for 4 hr and evaporated under reduced pressure. The residue is partitioned between chloroform and saturated sodium bicarbonate. The organic phase is collected, dried and evaporated to give 8.8 g of the title compound, ir ($CHCl_3$) 1753, 1742, 1715(broad), 1595 and 1100 cm^{-1} and nmr ($CDCl_3$) δ 1.78(s), 5.45(s), 6.29(s), 7.42(m), 7.84 (doublet of triplets) and 8.60(m).

(b) The title compound (18 g) is dissolved in acetone (20 ml) and a solution of hydrogen chloride in diethyl ether is added until precipitation is complete. The solvent is decanted and the residue is triturated with diethyl ether. The residue is crystallized from acetone to obtain the hydrochloride salt (15 g) of the title compound, mp 124-125°C. ANAL: Calculated for $C_{18}H_{15}NO_4$.HCl: C,62.52; H, 4.66; N, 4.05%; Found: C,62.30; H, 4.53; N, 3.94%.

(c) A solution of the title compound in diethyl ether and a solution of a half molar of (E)-2-butenedioic acid in isopropanol are combined at -10°C. The resulting precipitate is filtered and crystallized from acetonitrile to obtain the hemi-(E)-2-butenedioate salt, mp 128-130°C, of the title compound.

(d) In the same manner but replacing 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid with an equivalent amount of another compound of formula I described in Example 4, the following compounds of formula I are obtained, respectively: 4,5-dihydro-5-(1-methylethyl)-4-oxo-5-phenylfuran-2-carboxylic acid 3-pyridinylmethyl ester; 5-(4-chlorophenyl)-4,5-dihydro-5-methyl-4-oxofuran-2-carboxylic acid 3-pyridinylmethyl ester, nmr($CDCl_3$) δ 1.77(s), 5.46(s), 6.29(s), 7.42(m), 7.86(m) and 8.70(m); 4,5-dihydro-5,5-dimethyl-4-oxofuran-2-carboxylic acid 3-pyridinylmethyl ester, mp 109-110°C; spiro[furan-5(4H),-1'(2'H)-naphthalene]-3',4'-dihydro-4-oxo-2-carboxylic acid 3-pyridinylmethyl ester; 5-butyl-5-ethyl-4,5-dihydro-4-oxofuran-2-carboxylic acid 3-pyridinyl-methyl ester; 4,5-dihydro-4-oxo-5,5-diphenyl-furan-2-carboxylic acid 3-pyridinylmethyl ester; 5-cyclohexyl-4,5-dihydro-4-oxo-5-propylfuran-2-carboxylic acid 3-pyridinylmethyl ester; 4,5-dihydro-5-ethoxymethyl-5-(3-methoxyphenyl)-4-oxofuran-2-carboxylic acid 3-pyridinylmethyl ester; 4,5-dihydro-5-(3,4-diethylphenyl)-5-(4-nitrophenyl)-4-oxofuran-2-carboxylic acid 3-pyridinyl-

methyl ester; 1,7-dioxaspiro[4,4]non-2-ene-4-oxo-2-carboxylic acid 3-pyridinylmethyl ester; 1-oxaspiro[4,5]-ded-2-ene-4-oxo-2-carboxylic acid 3-pyridinylmethyl ester; spiro[furan-5(4H), 1'-indan]-4-oxo-2-carboxylic acid 3-pyridinylmethyl ester; and 5-cyclopentyl-4,5-dihydro-5-(3-ethoxypropyl)-4-oxofuran-2-carboxylic acid 3-pyridinylmethyl ester.

EXAMPLE 7

6-Methyl-6-phenyltetrahydropyran-2,3,5-trione (XI:R^2= Me, R^1 = Ph and R^3 = H)

To a stirred suspension of sodium hydride (10.5 g 54% in mineral oil) in dry tetrahydrofuran (400 ml) is added dropwise a solution of diethyl oxalate (16 g) and 3-hydroxy-3-phenyl-2-butanone (16.4 g described in Example 3) in tetrahydrofuran (50 ml). The solution temperature is maintained at 55-60°C, and the solution is maintained at this temperature for 18 hr after the addition is completed. The cold reaction mixture is poured into water and the mixture is adjusted pH 8 to 9 with sodium hydroxide or hydrochloric acid. This mixture at pH 8 to 9 is allowed to stand for 24 hr and extracted with diethyl ether. The ether extract is dried, evaporated and crystallized from diethyl ether to obtain the title compound: mp 142-144°C; ir(nujol) 3130, 1718 and 1640 cm^{-1}; uv (MeOH) λ_{max} 268nm(ϵ = 8830) and nmr ($MeOH-d_3$) δ 1.89 (s), 5.92 (s) and 7.34 (s).
Anal. Calculated for $C_{12}H_9O_4$: C, 66.05; H, 4.62%

Found: C, 66.14; H, 4.83%.

EXAMPLE 8

4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid (I:R^2 = Me, R^1 = Ph, and R^3 and R^4 = H)

A mixture of 6-methyl-6-phenyltetrahydropyran-2,3,5-trione (2.18 g, described in Example 7) in aqueous

sodium hydroxide (15 ml) at pH 11 is stirred for 24 hr and washed with diethyl ether. Hydrochloric acid (6N) is added until the solution becomes acidic at pH 1 to 4. The precipitate is collected and crystallized from diethyl ether to obtain the title compound (2.0 g), mp 174-176°C.

EXAMPLE 9

Optical Resolution of 4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid.

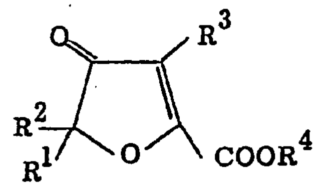
A solution of (+)-α-methyl benzylamine (3.63 g) in diethyl ether (50 ml) is added to a solution of 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid (6.54 g, described in Example 4) in 200 ml of 10% isopropyl alcohol in diethyl ether. The mixture is cooled and the crystals (6.5 g)are collected while saving the mother liquor. The crystals are recrystallized three times from methanol to obtain 5.0 g of the benzylamine salt having a constant rotation of $[\alpha]_D^{25} = +110^\circ$ (C=2, methanol) and mp 194-196°C. The latter salt (5.0 g) is stirred into water (100 ml) and diethyl ether (100 ml), and then 6N hydrochloric acid is added until the solution is acidic (pH 1). The ether phase is collected, washed with water until the washings are neutral, dried, evaporated and recrystallized from diethyl ether to give (+)-4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid (2.7 g): mp 87-89°C; $[\alpha]_D^{25} = +146.4^\circ$ (C=2, methanol); ir (nujol) 3440, 3320, 2540, 2440, 1720 and 1669 cm^{-1}; and Anal Calcd. for $C_{12}H_{10}O_4 \cdot H_2O$: C, 61.01%, H, 5.12%,water, 7.62% and Found: C, 61.19%, H, 5.07%,water, 7.85%.

The mother liquors, obtained from the above benzylamine salt, are evaporated. The residue (4.3 g) is dissolved in a solution of water (50 ml) and diethyl ether (50 ml) and 6N hydrochloric acid is added dropwise until the water layer is acidic (pH 1). The ether layer

is collected, washed with water until the washings are neutral, dried over magnesium sulfate and evaporated. The residue (2.7 g) is dissolved in 70 ml of 10% isopropyl alcohol- diethyl ether solution and a solution of (-)-α-methyl benzylamine in diethyl ether is added. The solution is cooled and the crystlas (3.9 g) are collected and recrystallized three times from methanol to obtain 2.4 g of the benzylamine salt having a constant rotation of $[\alpha]_D^{25} = -108^o$ (C=2, methanol) and mp 198-199°C. The latter salt (2.4 g) is stirred into water (70 ml) and diethyl ether (70 ml), and 6N hydrochloric acid is added until the water phase is acidic (pH 1). The ether phase is separated, washed with water until the washings are neutral and evaporated to give 1.6 g of residue. The residue is recrystallized from diethyl ether to give 1.2 g of (-)-4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid: mp 87-89°C; $[\alpha]_D^{25} = -144.1^o$ (C=2,methanol); ir (nujol) 3440, 3320, 2540, 1720 and 1669 cm^{-1}; Anal.Calcd. for $C_{12}H_{10}O_4 \cdot H_2O$: C, 61.01% H, 5.12%,water, 7.62% and Found: C, 61.14%, H, 5.05%, water, 5.82%.

CLAIMS

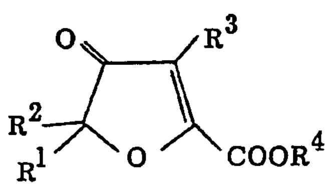
1. A compound of formula I



(I)

in which R^1 and R^2 each is lower alkyl, cyclo(lower)alkyl, lower alkoxy(lower)-alkylene, phenyl or phenyl mono- or disubstituted with lower alkyl, lower alkoxy, halo, nitro or trifluoromethyl; or R^1 and R^2 together form a $-(CH_2)_m-X-(CH_2)_n-$ chain wherein m and n each is an integer from one to four and X is methylene, oxa or thia; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 or spiro[indan]-1 radical; R^3 is hydrogen or lower alkyl; and R^4 is hydrogen, lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl-(lower)alkylene, or a therapeutically acceptable addition salt thereof.

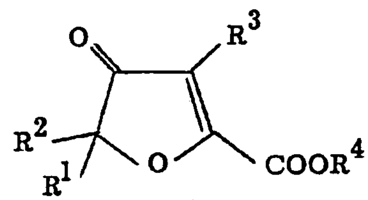
2. A compound of formula I



(I)

in which R^1 is lower alkyl, phenyl or phenyl monosubstituted with halo; R^2 is lower alkyl; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 radical; R^3 is hydrogen; and R^4 is hydrogen, lower alkyl or 3-pyridinyl(lower)alkylene, or a therapeutically acceptable addition salt thereof.

3. A compound of formula I



(I) .

in which R^1 is lower alkyl, phenyl or 4-chlorophenyl; R^2 is lower alkyl; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro-[1,2,3,4-tetrahydronaphthalene]-1 radical; R^3 is hydrogen; and R^4 is hydrogen, lower alkyl or 3-pyridinylmethyl, or a therapeutically acceptable addition salt thereof.

4. 4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid, as claimed in Claim 1.

5. 4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid benzylamine salt, as claimed in Claim 1.

6. 4,5-Dihydro-5,5-dimethyl-4-oxofuran-2-carboxylic acid, as claimed in Claim 1.

7. 5-(4 - Chlorophenyl)- 4,5-dihydro-5-methyl-4-oxofuran-2-carboxylic acid, as claimed in Claim 1.

8. 4,5 - Dihydro-5-(1 - methylethyl)-4-oxo-5-phenylfuran-2-carboxylic acid, as claimed in Claim 1.

9. Spiro[furan-5(4H),1'(2'H)-naphthalene]-3',4'-dihydro-4-oxo-2-carboxylic acid as claimed in Claim 1.

10. 4,5-Dihydro-5,5-dimethyl-4-oxofuran-2-carboxylic acid methyl ester, as claimed in Claim 1.

11. 4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid methyl ester, as claimed in Claim 1.

12. 4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid 3-pyridinylmethyl ester, as claimed in Claim 1.

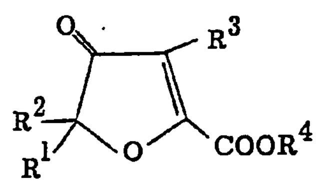
13. 4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid 3-pyridinylmethyl ester hydrochloride salt, as claimed in Claim 1.

14. 4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid 3-pyridinylmethyl ester hemi-(E)-2-butenedioate salt, as claimed in Claim 1.

15. 4,5-Dihydro-5,5-dimethyl-4-oxofuran-2-carboxylic acid 3-pyridinylmethyl ester, as claimed in Claim 1.

16. 5-(4-Chlorophenyl)-4,5-dihydro-5-methyl-4-oxofuran-2-carboxylic acid 3-pyridinylmethyl ester, as claimed in Claim 1.

17. A process for preparing a compound of formula I



(I)

in which R^1 and R^2 each is lower alkyl, cyclo(lower)alkyl, lower alkoxy(lower)-alkylene, phenyl or phenyl mono- or disubstituted with lower alkyl, lower alkoxy, halo, nitro or trifluoromethyl; or R^1 and R^2 together form a $-(CH_2)_m-X-(CH_2)_n-$ chain wherein m and n each is an integer from one to four and X is methylene, oxa or thia; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 or spiro[indan]-1 radical; R^3 is hydrogen or lower alkyl; and R^4 is hydrogen, lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower)alkylamino(lower)alkylene or 3-pyridinyl(lower)-alkylene, which comprises:

cyclizing a compound of formula X

$$R^1-\underset{\displaystyle OH}{\overset{\displaystyle R^2}{\underset{|}{\overset{|}{C}}}}-CO-CH(R^3)-CO-COOH \qquad (X)$$

in which R^1, R^2 and R^3 are as defined herein under acidic conditions to obtain the corresponding compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen, and, if desired,

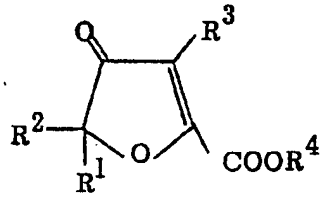
esterifying the latter compound of formula I to obtain the corresponding compound of formula I in wnich R^1, R^2 and R^3 are as defined herein and R^4 is lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl(lower)alkylene.

18. A process according to Claim 17, wherein R^1 is lower alkyl, phenyl or phenyl monosubstituted with halo; R^2 is lower alkyl; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 radical; R^3 is hydrogen; and R^4 is hydrogen, lower alkyl or 3-pyridinyl(lower)alkylene.

19. A process, as claimed in Claim 17, wherein said acidic conditions is selected from an inert organic solvent or aqueous solution containing hydrogen chloride, hydrogen bromide, hydrochloric acid, hydrobromic acid, p-toluenesulfonic acid, sulfuric acid, phosphoric acid or polyphosphoric acid.

20. The process of Claim 17 for the synthesis of a therapeutically acceptable addition salt of said compound of formula I in which R^1, R^2 and R^3 are as defined therein and R^4 is hydrogen, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl-(lower)alkylene, wherein said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen is reacted with a therapeutically acceptable organic or inorganic base to obtain the corresponding therapeutically acceptable organic or inorganic base addition salt of said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen; or said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)-amino(lower)alkylene or 3-pyridinyl(lower)alkylene is reacted with a therapeutically acceptable acid to obtain the corresponding therapeutically acceptable acid addition salt of said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is amino(lower)alkylene, lower alkylamino(lower)-alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl(lower)alkylene.

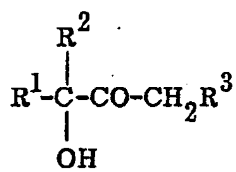
21. A process for preparing a compound of formula I



(I)

in which R^1 and R^2 each is lower alkyl, cyclo(lower)alkyl, lower alkoxy(lower)-alkylene, phenyl or phenyl mono- or disubstituted with lower alkyl, lower alkoxy, halo, nitro or trifluoromethyl; or R^1 and R^2 together form a $-(CH_2)_m-X-(CH_2)_n-$ chain wherein m and n each is an integer from one to four and X is methylene, oxa or thia; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 or spiro[indan]-1 radical; R^3 is hydrogen or lower alkyl; and R^4 is hydrogen, lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)alkylene, lower alkyl-amino(lower)alkylene, di(lower)alkylamino(lower)alkylene or 3-pyridinyl(lower)-alkylene, which comprises:

reacting a compound of formula II



(II)

in which R^1, R^2 and R^3 are as defined herein with a di(lower alkyl)oxalate in the presence of a strong inorganic proton acceptor under anhydrous conditions, hydrolyzing the mixture with water at about pH 10 to about pH 12, and allowing the latter mixture to stand under acidic conditions to obtain the corresponding compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen; and if desired,

esterifying the latter compound of formula I to obtain the corresponding compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl(lower)alkylene.

22. A process according to Claim 21, wherein R^1 is lower alkyl, phenyl or phenyl monosubstituted with halo; R^2 is lower alkyl; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 radical; R^3 is hydrogen and R^4 is hydrogen, lower alkyl or 3-pyridinyl(lower)alkylene.

23. A process, as claimed in Claim 21, wherein acidic conditions is obtained by the addition of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid or polyphosphoric acid.

24. A process, as claimed in Claim 21, wherein said strong inorganic proton acceptor is sodium hydride.

25. A process, as claimed in Claim 21, wherein said di(lower alkyl)oxalate is selected from dimethyl oxalate or diethyl oxalate.

26. The process of Claim 21 for the synthesis of a therapeutically acceptable addition salt of said compound of formula I in which R^1, R^2 and R^3 are as defined therein and R^4 is hydrogen, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl-(lower)alkylene, wherein said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen is reacted with a therapeutically acceptable organic or inorganic base to obtain the corresponding therapeutically acceptable organic or inorganic base addition salt of said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen; or said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)-amino(lower)alkylene or 3-pyridinyl(lower)alkylene is reacted with a therapeutically acceptable acid to obtain the corresponding therapeutically acceptable acid addition salt of said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl(lower)alkylene.

27. A method of lowering lipid levels in a mammal, which comprises administering to said mammal an effective hypolipidemic amount of a compound of formula I or a therapeutically acceptable addition salt thereof, as claimed in Claim 1, 2 or 3.

28. A pharmaceutically composition comprising a compound of formula I or a therapeutically acceptable salt thereof, as claimed in Claim 1, 2 or 3 and a pharmaceutically acceptable carrier.

29. A method of lowering lipid levels in a mammal, which comprises administering to the mammal an effective hypolipidemic amount of a compound of formula I, or a therapeutically acceptable salt thereof, in combination with an effective hypolipidemic amount of clofibrate.

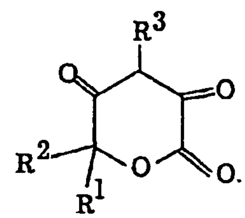
30. A method as claimed in Claim 29 wherein said compound of formula I is 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid 3-pyridinylmethyl ester, or the hydrochloric acid addition salt thereof, or the hemi-(E)-2-butenedioate salt thereof.

31. A method as claimed in Claim 29 wherein said compound of formula I, or a therapeutically acceptable salt thereof, is adminstered sequentially or simultaneously with clofibrate.

32. A pharmaceutical composition comprising clofibrate, a compound of formula 1, or a therapeutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

33. A pharmaceutical composition as claimed in Claim 32 wherein said compound of formula I is 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid 3-pyridinylmethyl ester, or the hydrochloric acid addition salt thereof, or the hemi-(E)-2-butenedioate salt thereof.

34. A compound of formula XI



(XI)

in which R^1 and R^2 each is lower alkyl, cyclo(lower)alkyl, lower alkoxy(lower)-alkylene, phenyl or phenyl mono- or disubstituted with lower alkyl, lower alkoxy, halo, nitro or trifluoromethyl; or R^1 and R^2 together form a $-(CH_2)_m-X-(CH_2)_n-$chain wherein m and n each is an integer from one to four and X is methylene, oxa or thia; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 or spiro[indan]-1 radical; and R^3 is hydrogen or lower alkyl.

35. A compound of formula XI, as claimed in Claim 34, wherein R^1 is lower alkyl, phenyl or phenyl monosubstituted with halo; R^2 is lower alkyl; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 radical; and R^3 is hydrogen.

36. A compound of formula XI, as claimed in Claim 34, wherein R^1 is lower alkyl, phenyl or 4-chlorophenyl; R^2 is lower alkyl; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 radical; and R^3 is hydrogen.

37. 6-Methyl-6-phenyltetrahydropyran-2,3,5-trione, as claimed in Claim 36.

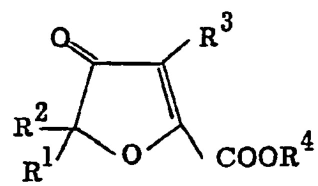
38. (+)-4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid, as claimed in Claim 1.

39. (-)-4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid, as claimed in Claim 1.

AMENDED CLAIMS

(received by the International Bureau on 1 November 1979 (01.11.79))

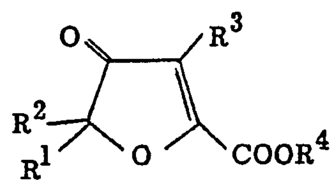
1. A compound of formula I



(I)

in which R^1 and R^2 each is lower alkyl, cyclo(lower)alkyl, lower alkoxy(lower)-alkylene, phenyl or phenyl mono- or disubstituted with lower alkyl, lower alkoxy, halo, nitro or trifluoromethyl; or R^1 and R^2 together form a $-(CH_2)_m-X-(CH_2)_n-$ chain wherein m and n each is an integer from one to four and X is methylene, oxa or thia; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 or spiro[indan]-1 radical; R^3 is hydrogen or lower alkyl; and R^4 is hydrogen, lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)alkylene, lower alkyl-amino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl-(lower)alkylene, or a therapeutically acceptable addition salt thereof.

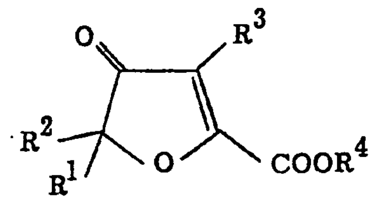
2. A compound of formula I



(I)

in which R^1 is lower alkyl, phenyl or phenyl monosubstituted with halo; R^2 is lower alkyl; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 radical; R^3 is hydrogen; and R^4 is hydrogen, lower alkyl or 3-pyridinyl(lower)alkylene, or a therapeutically acceptable addition salt thereof.

3. A compound of formula I



(I)

in which R^1 is lower alkyl, phenyl or 4-chlorophenyl; R^2 is lower alkyl; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro-[1,2,3,4-tetrahydronaphthalene]-1 radical; R^3 is hydrogen; and R^4 is hydrogen, lower alkyl or 3-pyridinylmethyl, or a therapeutically acceptable addition salt thereof.

4. 4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid, as claimed in Claim 1.

5. 4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid benzylamine salt, as claimed in Claim 1.

6. 4,5-Dihydro-5,5-dimethyl-4-oxofuran-2-carboxylic acid, as claimed in Claim 1.

7. 5-(4 - Chlorophenyl)- 4,5-dihydro-5-methyl-4-oxofuran-2-carboxylic acid, as claimed in Claim 1.

8. 4,5 - Dihydro-5-(1 - methylethyl)-4-oxo-5-phenylfuran-2-carboxylic acid, as claimed in Claim 1.

9. Spiro[furan-5(4H),1'(2'H)-naphthalene]-3',4'-dihydro-4-oxo-2-carboxylic acid as claimed in Claim 1.

10. 4,5-Dihydro-5,5-dimethyl-4-oxofuran-2-carboxylic acid methyl ester, as claimed in Claim 1.

11. 4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid methyl ester, as claimed in Claim 1.

12. 4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid 3-pyridinylmethyl ester, as claimed in Claim 1.

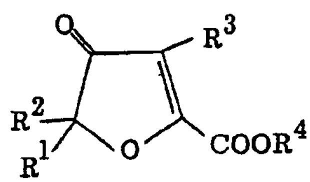
13. 4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid 3-pyridinylmethyl ester hydrochloride salt, as claimed in Claim 1.

14. 4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid 3-pyridinylmethyl ester hemi-(E)-2-butenedioate salt, as claimed in Claim 1.

15. 4,5-Dihydro-5,5-dimethyl-4-oxofuran-2-carboxylic acid 3-pyridinylmethyl ester, as claimed in Claim 1.

16. 5-(4-Chlorophenyl)-4,5-dihydro-5-methyl-4-oxofuran-2-carboxylic acid 3-pyridinylmethyl ester, as claimed in Claim 1.

17. A process for preparing a compound of formula I



(I)

in which R^1 and R^2 each is lower alkyl, cyclo(lower)alkyl, lower alkoxy(lower)-alkylene, phenyl or phenyl mono- or disubstituted with lower alkyl, lower alkoxy, halo, nitro or trifluoromethyl; or R^1 and R^2 together form a $-(CH_2)_m-X-(CH_2)_n-$ chain wherein m and n each is an integer from one to four and X is methylene, oxa or thia; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 or spiro[indan]-1 radical; R^3 is hydrogen or lower alkyl; and R^4 is hydrogen, lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower)alkylamino(lower)alkylene or 3-pyridinyl(lower)-alkylene, which comprises:

cyclizing a compound of formula X

$$R^1-\overset{\displaystyle R^2}{\underset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}-CO-CH(R^3)-CO-COOH \qquad (X)$$

in which R^1, R^2 and R^3 are as defined herein under acidic conditions to obtain the corresponding compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen, and, if desired,

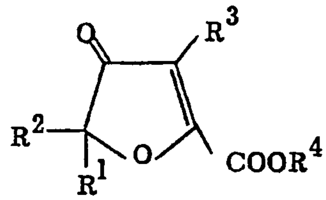
esterifying the latter compound of formula I to obtain the corresponding compound of formula I in wnich R^1, R^2 and R^3 are as defined herein and R^4 is lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl(lower)alkylene.

18. A process according to Claim 17, wherein R^1 is lower alkyl, phenyl or phenyl monosubstituted with halo; R^2 is lower alkyl; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 radical; R^3 is hydrogen; and R^4 is hydrogen, lower alkyl or 3-pyridinyl(lower)alkylene.

19. A process, as claimed in Claim 17, wherein said acidic conditions is selected from an inert organic solvent or aqueous solution containing hydrogen chloride, hydrogen bromide, hydrochloric acid, hydrobromic acid, p-toluenesulfonic acid, sulfuric acid, phosphoric acid or polyphosphoric acid.

20. The process of Claim 17 for the synthesis of a therapeutically acceptable addition salt of said compound of formula I in which R^1, R^2 and R^3 are as defined therein and R^4 is hydrogen, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl(lower)alkylene, wherein said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen is reacted with a therapeutically acceptable organic or inorganic base to obtain the corresponding therapeutically acceptable organic or inorganic base addition salt of said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen; or said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl(lower)alkylene is reacted with a therapeutically acceptable acid to obtain the corresponding therapeutically acceptable acid addition salt of said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl(lower)alkylene.

21. A process for preparing a compound of formula I



(I)

in which R^1 and R^2 each is lower alkyl, cyclo(lower)alkyl, lower alkoxy(lower)-alkylene, phenyl or phenyl mono- or disubstituted with lower alkyl, lower alkoxy, halo, nitro or trifluoromethyl; or R^1 and R^2 together form a $-(CH_2)_m-X-(CH_2)_n-$ chain wherein m and n each is an integer from one to four and X is methylene, oxa or thia; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 or spiro[indan]-1 radical; R^3 is hydrogen or lower alkyl; and R^4 is hydrogen, lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower)alkylamino(lower)alkylene or 3-pyridinyl(lower)-alkylene, which comprises:

reacting a compound of formula II

$$R^1-\overset{\displaystyle R^2}{\underset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}-CO-CH_2R^3 \qquad \text{(II)}$$

in which R^1, R^2 and R^3 are as defined herein with a di(lower alkyl)oxalate in the presence of a strong inorganic proton acceptor under anhydrous conditions, hydrolyzing the mixture with water at about pH 10 to about pH 12, and allowing the latter mixture to stand under acidic conditions to obtain the corresponding compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen; and if desired,

esterifying the latter compound of formula I to obtain the corresponding compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is lower alkyl, cyclo(lower)alkyl, phenyl(lower)alkylene, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl(lower)alkylene.

22. A process according to Claim 21, wherein R^1 is lower alkyl, phenyl or phenyl monosubstituted with halo; R^2 is lower alkyl; or R^1 and R^2 together with the carbon atom to which they are joined form a spiro[1,2,3,4-tetrahydronaphthalene]-1 radical; R^3 is hydrogen and R^4 is hydrogen, lower alkyl or 3-pyridinyl(lower)alkylene.

23. A process, as claimed in Claim 21, wherein acidic conditions is obtained by the addition of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid or polyphosphoric acid.

24. A process, as claimed in Claim 21, wherein said strong inorganic proton acceptor is sodium hydride.

25. A process, as claimed in Claim 21, wherein said di(lower alkyl)oxalate is selected from dimethyl oxalate or diethyl oxalate.

26. The process of Claim 21 for the synthesis of a therapeutically acceptable addition salt of said compound of formula I in which R^1, R^2 and R^3 are as defined therein and R^4 is hydrogen, amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl-(lower)alkylene, wherein said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen is reacted with a therapeutically acceptable organic or inorganic base to obtain the corresponding therapeutically acceptable organic or inorganic base addition salt of said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is hydrogen; or said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)-amino(lower)alkylene or 3-pyridinyl(lower)alkylene is reacted with a therapeutically acceptable acid to obtain the corresponding therapeutically acceptable acid addition salt of said compound of formula I in which R^1, R^2 and R^3 are as defined herein and R^4 is amino(lower)alkylene, lower alkylamino(lower)alkylene, di(lower alkyl)amino(lower)alkylene or 3-pyridinyl(lower)alkylene.

27. A method of lowering lipid levels in a mammal, which comprises administering to said mammal an effective hypolipidemic amount of a compound of formula I or a therapeutically acceptable addition salt thereof, as claimed in Claim 1, 2 or 3.

28. A pharmaceutically composition comprising a compound of formula I or a therapeutically acceptable salt thereof, as claimed in Claim 1, 2 or 3 and a pharmaceutically acceptable carrier.

29. A method of lowering lipid levels in a mammal, which comprises administering to the mammal an effective hypolipidemic amount of a compound of formula I, or a therapeutically acceptable salt thereof, in combination with an effective hypolipidemic amount of clofibrate.

30. A method as claimed in Claim 29 wherein said compound of formula I is 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid 3-pyridinylmethyl ester, or the hydrochloric acid addition salt thereof, or the hemi-(E)-2-butenedioate salt thereof.

31. A method as claimed in Claim 29 wherein said compound of formula I, or a therapeutically acceptable salt thereof, is adminstered sequentially or simultaneously with clofibrate.

32. A pharmaceutical composition comprising clofibrate, a compound of formula I, or a therapeutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

33. A pharmaceutical composition as claimed in Claim 32 wherein said compound of formula I is 4,5-dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid 3-pyridinylmethyl ester, or the hydrochloric acid addition salt thereof, or the hemi-(E)-2-butenedioate salt thereof.

34. (+)-4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid, as claimed in Claim 1.

35. (-)-4,5-Dihydro-5-methyl-4-oxo-5-phenylfuran-2-carboxylic acid, as claimed in Claim 1.

INTERNATIONAL SEARCH REPORT

WO 80/00325

International Application No PCT/US79/00376

1/4

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC

INT.CL. C07D 495/10;405/12, 307/68,493/10;A61K 31/34,31/38, 31/44;US.CL.260/343.5,345.7R,345.8R,347.3,347.5;546/15,283;... ~~549/1,9,13,60, 88; 424/263, 276; 424/283, 285~~

II. FIELDS SEARCHED

Minimum Documentation Searched

Classification System	Classification Symbols
US	260/343.5, 345.7R, 345.8R, 347.3, 347.5; 546/15,283; 549/1,9,13,60, 88; 424/263, 276, 283, 285.

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched

Chemical Abstracts-Vols 76-89,2-(or 3) furancarboxylic acid,4,5-dihydro, Vols 31 to 75 2-(or 3) furoic acid, Vols 1-30,pyromucic acid;Vols 66-89,2H-Pyran-2.5(6H)-dione,3-hydroxy;Vols 1-65. Hexenoic acid,5-hydroxy,δ-lactone and valeric acid,5-hydroxy-δ-lactone

III. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X,A	N,Chemical Abstracts, Vol.81,No.15,issued 14 Oct. 1974 14(Columbus,Ohio, U.S.A)Gelin et al., "Synthesis and behavior of 4-(ethoxycarbonyl)-3(2H)-furanones." See Page 441, Column 2, the abstract No. 91276f, Bull. Soc. Chim. Fr. 1974, (5-6, pt. 2). 1043-7 (Fr).	1-16,38-39
X,A	DE. A, 2359891 Published 28 June 1974	1-16,38-39
X,A	N, Chemical Abstracts, Vol.79, No. 1, issued 09 July 1973(Columbus, Ohio U.S.A) Krutosikova et al.,"Preparation of substituted 5-phenyl-2-furfuryl bromides, isothiocyanates and thiocyanates" see Page 439, Column 2, the abstract No. 5193f,Chem.Lett. 1973, (4), 425-6 (Eng).	1-16,38-39
X,A	N, Chemical Abstracts, Vol. 79.No.13,issued 01 Oct. 1973 (Columbus, Ohio,U.S.A), DeRijke et al.,"Synthesis and Reactions of 3-oxo-2H-furan derivatives"	1-16,38-39

* Special categories of cited documents:

"A" document defining the general state of the art

"E" earlier document but published on or after the international filing date

"L" document cited for special reason other than those referred to in the other categories

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but on or after the priority date claimed

"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention

"X" document of particular relevance

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11 SEPTEMBER 1979	26 SEP 1979
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Natalie Trousof

	See page 469, Column 2, the abstract No.78489S,Recl. Trav. Chim . Pays-Bas.1973, 92(6) 731-8 (Eng).	
X,A	N, Chemical Abstracts, Vol. 78,No. 5, issued 05 Febt. 1973 (Columbus, Ohio,USA) Galliand. et al., "Acylation of β-dicarbonyl compounds by α -chlorinated acid chlorides. Synthesis of 3-acyl-or 3-ethoxycarbonyl-4-oxo-4.5-dihydro furans and 3-acyltetronic acids". See page 481, col. 2, the abstract no. 29518W, C.R. Acad. Sci, Ser. C 1972, 275 (16), 897-900 (Fr.).	1-16 38-39
X,A	R.E. Rosenkranz et al. Helv. Chim.Acta, vol. 46, published 1963. See page 1259 to 1285, especially pages 1266,1267, 1270 and 1272.	1-16,38-39
X,A	N, Chemical Abstracts,Vol. 87. No. 13,issued 26 Sept. 1977 '26 (Columbus Ohio USA) Chantegrel "Synthesis and Structure of 2-N-arylamino methylene-4-ethoxycarbonyl -5-methyl-3-[2H]furanones. See page 599. Col. 2, the abstract No. 87:102101X,J Chemical Res. S(synopses)1977.(5), 127(Eng)	1-16 38-39
X,A	N,Chemical Abstracts, Vol. 88, No.5 issued 30 Jan. 1978 (Columbus, OhioUSA). Reffstrup et al ., "Synthesis of bullatenone and bullatenone- related substances." See page 478, Column 1, the abstract No. 88:37534V, Acta Chem. Scand. Ser. B 1977, B31(8), 727-9 (Eng.).	1-16,38-39
X,A	US A, 3,439,000 published 15 April 1969 , Wyckoff et al.	17-20
X,A	US A, 3,442,913 published 06 May 1969 , Wyckoff et al.	17-20
X,A	US A 2,745,845 published 15 May 1956 , Jones et al.	17-20
X,A	US A, 3,644,399 published 22 February 1972 , Brown et al.	17-20
X,A	US A, 2,744,917 published 08 May 1956 , Jones et al.	17-20
X,A	US A, 3,743,656 published 03 July 1973 , Brown et al.	17-20

X,A	* BE A, 764464 published 18 March 1971	27-33
A	US A, 4,000,164 published 28 Dec. 1976, Parker.	27,29-31
X,P	N, Chemical Abstracts, Vol. 89, No. 23, issued 04 Dec. 1978 (Columbus, Ohio, U.S.A.), Pehr et al., "Reaction of D-glucose with diethylammonium tartrate: isolation of 3.5-dihydroxy-6-methyl-2H-pyran-2-one and the detection of cyclic amino reductones as reductione methyl ethers." See page 660, column 1, the abstract No. 89: 1978 25q, carbohydr. Res. 1978, 64, 1-7 (Ger).	34-37
X	US A, 3,344,150 published 26 Sept. 1967, Cais et al.	34-37
X	US A. 3,393,206 published 16 July 1968, Cais et al.	34-37
X	US A, 3,393,205 published 16 July 1968 Cais et al.	34-37
X	US A, 3,393,204 published 16 July 1968 Cais et al.	34-37
X	N, Chemical Abstracts, Vol. 83, No. 21 issued 24 November 1975 (Columbus, Ohio U.S.A) Lohrisch et al. "Fungus pigments 24 synthesis of Grevillin C and related 2H-pyran-2,5(6H)-diones." See page 543, Column 1, the abstract No. 178710h, Tetrahedron Letters 1975, (33), 2905-8 (Ger).	34-37

International Application No. PCT/US79/000376

4/4

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ______, because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers ______, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

Invention I: Claims 1-16, 27-33 and 38-39
Invention II: Claims 17-20
Invention III: Claims 21-26
Invention IV: Claims 34-37

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.